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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,078	01/08/2004	David H. Reifsnyder	12441.00050/16331.004	6550

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Intellectual Property
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EXAMINER

CARLSON, KAREN C

ART UNIT	PAPER NUMBER
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1656

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/753,078	Applicant(s) REIFSNYDER ET AL.	
	Examiner Karen Cochran Carlson	Art Unit 1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on June 17, 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-57 is/are pending in the application.
- 4a) Of the above claim(s) 20-49 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19, 50-57 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1656

This Office Action is in response to the papers filed June 17, 2009.

Claims 1-57 are pending. Claims 20-49 are withdrawn. Thus, claims 1-19 and 50-57 are pending and under examination.

Benefit of priority is to August 13, 2003.

Maintenance of Rejections:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-18, 50-56 are again rejected under 35 U.S.C. 102(b) as being anticipated by Diaz-Collier et al. (1993; EP 0 559 632).

Diaz-Collier et al. teach that a ala-TFPI preparation refolded and purified by the method disclosed in Example 1 (page 6+ and esp page 6, para. 2 regarding Ala-TFPI). This TFPI preparation was greater than 95% homogeneous (page 12, line 2), suggesting that there was less than 5% misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts of the TFPI. There is also no evidence or indication that the preparation contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated.

Art Unit: 1656

While 10-18 and 56 are drawn to large scale pharmaceutical preparations of TFPI, these claims are included in this rejection because the pharmaceutical carrier is not designated.

Absent evidence to the contrary, it appears that the preparation is patentably indistinguishable from that of the present claims.

There is sufficient evidence that the product disclosed by the reference is Applicants' product, and the burden is shifted to Applicants to distinguish the two. See *In re Best*, 195 USPQ 430 and *Ex Parte Gray* 10 USPQ 2d 1922, 1923.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 10-19, 56, and 57 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Diaz-Collier et al. (1993; EP 0 559 632) in view of Chen et al. (February 25, 2003, priority to 1999; U.S. 6,525,102).

Diaz-Collier et al. teach ala-TFPI preparations refolded and purified by the method disclosed in Example 1 (page 6+ and esp. page 6, para. 2 regarding Ala-TFPI). This TFPI preparation was greater than 95% homogeneous (page 12, line 2), suggesting that there was less than 5% misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts of the TFPI. There is also no evidence or

Art Unit: 1656

indication that the preparation contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated.

Diaz Collier et al. do not teach that the pharmaceutical compositions comprising 20mM sodium citrate, 300 mM L-arginine, and 5 mM methionine, pH 5.5. However, at page 3, para. 2, Diaz-Collier et al. teach that an advantage of their inventions is that the TFPI has substantially greater homogeneity than TFPI obtained in mammalian SK hepatoma cells and list 3 advantages of TFPI produced in E. coli (page 3, paras, 3, 4, and 5): A) no phosphorylation of TFPI, B) less proteolytic internal cleavages, and C) no glycosylation of TFPI.

Chen et al. teach a preparation comprising TFPI in 10mM sodium citrate and 300 mM arginine buffer at pH 5.5 (Col. 3, lines 41-45; Example 8). At Col. 10, lines 21+, Chen et al. teach to stabilize the pharmaceutical composition with methionine to protect TFPI from oxidation. Chen et al. teach that the addition of arginine to a TFPI preparation protects TFPI from aggregation (Col. 6, lines 8-55).

Therefore, it would have been obvious to one of ordinary skill in the art make pharmaceutical compositions comprising sodium citrate, L-arginine, and methionine and the TFPI produced by Diaz-Collier et al. because Diaz-Collier et al. teach that their preparation of TFPI is 95% homogeneous and is not phosphorylated or glycosylated over the prior art preparations of TFPI and Chen et al. teach that pharmaceutical compositions of TFPI comprising sodium citrate, L-arginine, and methionine are useful to administer TFPI in a clinical setting.

Art Unit: 1656

Applicants argue at page 16 of their response that Diaz-Collier et al. do not teach commercial-scale preparations and pharmaceutical formulations comprising TFPI and TFPI analogs do not meet commercial grade standards of purity, that is, less than 12% modified species or commercial scale quantity of at least 200 grams. In response, Diaz-Collier et al. state that their preparation of TFPI is at least 95% homogeneous; therefore, one can only conclude that there are less than 5% modified species in the preparation taught by Diaz-Collier et al.

Applicants discuss Examples I and II of Diaz-Collier; Example II is not part of the rejection and is an alternative purification method for TFPI relative to Example I. Therefore, the Examiner will not discuss Example II because Example II is not cited as anticipating the claimed invention.

Applicants urge (page 17) that the TFPI products produced in Example I comprise a large dimer content. It is noted that the passage of Diaz-Collier cited by applicants at page 11, lines 37-40 states that the TFPI dimer content produced by Example I is higher than TFPI dimer content produced by Example II. No statement is made by Diaz-Collier regarding the % TFPI dimer content of the product of Example I; however, Applicants speculate that the dimer content appears to be above 12% and this speculation is without merit. It is noted that Claim 1, for example, does not exclude TFPI dimers, only that the TFPI and analogs thereof that are not oxidized, carbamylated, deamidated, comprise a cysteine adduct, aggregated, or misfolded be at least 88% of the product.

Note that dimerization is not aggregation; aggregation is a composite of misfolded proteins, while dimerization is a composite of correctly folded monomers.

Applicants note on page 19, line 6+. that the mass spectral results of Diaz-Collier do not provide any degree of certainty regarding the heterogeneity in the TFPI samples arise from oxidation, carbamylation, deamidation, comprise a cysteine adduct, aggregation, or misfolding. The Examiner agrees. The Examiner cannot make any speculations beyond the teachings of Diaz-Collier that the TFPI product of Example I is at least 95% homogeneous.

Applicants discuss inherency of anticipation at pages 19-20. It is noted that the rejection is not based on inherency, but on the teachings of Diaz-Collier that the TFPI product of Example I is at least 95% homogeneous.

These same arguments are referred to by Applicants in the discussion of the rejection of the claims under 35 USC 103 over the combined teachings of Diaz-Collier and Chen et al. Applicants assert that because Diaz-Collier do not teach the the claimed preparations, Chen et al. does not remedy the failed teachings. Applicants are referred to the discussion above regarding Diaz-Collier.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Art Unit: 1656

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson whose telephone number is 571-272-0946. The examiner can normally be reached on 6:00 AM - 4:00 PM, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1656

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen Cochrane Carlson, Ph.D./

Primary Examiner, Art Unit 1656